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Does Adjuvant Therapy with Omega-3 Fatty Acids (Fish Oil) Improve Joint Tenderness in Patients with Rheumatoid Arthritis?

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Does adjuvant therapy with Omega-3 fatty acids (fish oil) improve joint tenderness in patients with Rheumatoid Arthritis?

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not adjuvant therapy with Omega-3 fatty acids (fish oil) improves joint tenderness in patients with Rheumatoid Arthritis.

STUDY DESIGN: Review of 3 double-blind, randomized controlled trials from 2010- 2017.

DATA SOURCES: Three peer-reviewed journal articles written in English were found using PubMed. Articles were selected based on their relevance to the question and whether the outcome measured was patient-oriented evidence that matters.

OUTCOME(S) MEASURED: All articles analyzed the effectiveness of adjunctive treatment with omega-3 fatty acids on the improvement of joint tenderness in patients with rheumatoid arthritis. The overall outcome measured was the number of tender joints before and after treatment with omega-3 fatty acids in addition to traditional DMARD therapy.

RESULTS: All three studies found statistically significant improvement in joint tenderness with adjunctive treatment with omega-3 fatty acid supplementation. Different concentrations of fish oil containing EPA and DHA were administered to the treatment groups and compared to either a control or placebo group. Patients complied with the same traditional DMARD therapy in each individual study, though the therapies differed between studies.

CONCLUSIONS: This review provides evidence from three separate studies that fish oil supplementation decreases the number of tender joints in patients with active RA. Future research should focus on increasing sample size and generalizability of research findings, and determine the effectiveness of fish oil combined with different DMARD therapies.

KEY WORDS: Fish oils, Fatty acids, Omega-3, and Rheumatoid Arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive, symmetric, inflammatory arthritis affecting 1.3 million U.S adults, about 0.6% of the population.[1] Middle-aged women are affected two times more than men and pose the highest risk. [2] According to a study done in 2009, estimated the overall cost of care for RA patients was $39.2 billion.[3] In addition, a study in 2008 found that RA accounted for 36.5 million health care visits.[4] Although RA does have genetic associations, the cause is still not well understood despite years of research.

RA is an autoimmune condition causing an immune-mediated attack on joints leading to significant inflammation, pain, and decreased joint mobility and function. Most of the inflammation is caused by the proliferation of the joint synovium, where there is an accumulation of inflammatory immune cells such as neutrophils, CD4 helper T cells, B cells, and macrophages. Accumulation of inflammatory cells causes pain and swelling, further leading to the production and infiltration of inflammatory mediators such as tumor necrosis factor, interleukins, and prostaglandins.[5] Multiple joints are affected in a symmetric distribution throughout the body, where inflammation and immune-mediated reactions cause erosion of cartilage and bone in the joint space.[5]

Disease-modifying anti-rheumatic drug (DMARD) therapy remains the mainstay of treatment for rheumatoid arthritis, aimed at managing symptoms and decreasing joint destruction.[6] There are conventional, targeted, and biologic DMARD options which all are prescribed with the intent to minimize the inflammatory effects of this condition by targeting specific inflammatory molecules; drug examples include, methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, corticosteroids, Janus kinase inhibitors, tumor necrosis factor antagonists, interleukin-1 receptor antagonists, and interleukin-6 receptor antagonists.[7] In severe

cases, surgical joint replacement may be needed late in the disease.[7] Rheumatoid arthritis currently has no 'cure' through medical therapy. All of the medications listed above are only capable of decreasing disease severity and preventing further damage to joint margins. Each DMARD option comes with significant side effects that vary amongst individuals, such as hair loss, allergic reactions, gastrointestinal discomfort, mouth sores, hepatotoxicity, and more.[7] Harsh side effects and high risk of individualized adverse drug reactions from DMARD therapy have led to multiple clinical trials exploring alternate drug therapies, such as omega-3 fatty acids. Omega-3 fatty acids target different inflammatory molecules than traditional DMARD therapy, altering the innate inflammatory pathway at a different angle with less adverse side effects.[8]

Arachidonic acid (AA) is an omega-6 fatty acid that sits in the phospholipid bilayer of cell membranes.[8] AA can act as a precursor for many different enzymes involved in the inflammatory process such as prostaglandins and leukotrienes. Increased amounts of omega-3 fatty acids found in fish oil, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have an inhibitory effect on AA; thus leading to a decreased production of inflammatory molecules.[8] This mechanism of omega-3 fatty acid proliferation is the focus for determining the anti-inflammatory effects that adjunctive supplementation with fish oil has on individuals with RA.[8]

OBJECTIVE

The objective of this selective EBM review is to determine whether adjuvant therapy with omega-3 fatty acids (fish oil) improves joint tenderness in patients with rheumatoid arthritis.

METHODS:

All three studies were peer-reviewed journal articles written in English, dated from 2010-2017. Articles were selected using PubMed as a research database. Keywords used in the search

included, “Fish Oils," "Fatty acids," "Omega-3," and "Rheumatoid Arthritis." Inclusion criteria were as follows: Omega-3 fatty acid supplementation for previously diagnosed Rheumatoid Arthritis in an adult, randomized control trials within the past ten years, and measurement of the patient-oriented outcome of joint tenderness. Exclusion criteria were also the same for all three articles including children less than 18 years old, outcomes that were not patient-oriented, and an article that was not a double-blind, randomized control trial. Detailed descriptions of both inclusion and exclusion criteria for each individual study is provided in Table 1. The diagnosis of RA was based on criteria from the American Rheumatism Association, Association of Rheumatology America, and the American College of Rheumatology from the 2010 revision. Fish oil supplements, including varying concentrations of EPA and DHA, were used as the clinical intervention with a control group or a placebo group as a comparison. The summary of statistics used was both mean change from baseline and p-values.

OUTCOMES MEASURED:

This review focused on determining the mean change from baseline of the number of tender joints both before and after the intervention. Data collection in all articles was based on the subjective assessment by the patient of their total number of tender joints before and after the completion of the supplemental treatment. The Disease Assessment Score (DAS-28) takes into account tender joint count, erythrocyte sedimentation rate, and C-reactive protein levels. The visual analog scale (VAS) is a continuous scale that ranges from zero, signifying no pain, to 100, signifying excruciating pain.[5] Veselinovic et al. made assessments at baseline and at three months using the DAS-28 and VAS.[5] Rajaei et al. made assessments at baseline and every four weeks for three months using both DAS-28 and VAS.[6] Bahadori et al. made assessments at baseline and week one, two, four, 11, and 22 using a trained physician to manually palpate the

Table 1. - Demographics and Characteristics of Studies

Study	Type	# of Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Bahadori B, et al. 2010[9]	RCT	24	54-62	RA diagnosed according to the ACRA criteria.	Stable doses of MTX of at least 10 mg/week and of corticosteroids up to 10 mg/ day of prednisolone were required 1 month before enrollment.	11	0.20 g of fish oil per kg with a specific combination of EPA, DHA, α-linolenic acid, docosapentaenoic acid, or a placebo. All IV for 4 hours over 14 days.
Rajaei E, et al. 2015[6]	RCT	60	20-70	Clinical evaluation and diagnosis of RA. Exclusion criteria: Diagnosis > 6 months, bone deformities, metabolic and gastrointestinal diseases, medication dose fluctuation, use of Omega-3 fatty acids supplements, digestive problems & severe infection.	Exclusion Continued: AST, ALT, or Creatinine levels higher than 1.5 times the maximum normal limit, total bilirubin levels more than 1.8 mg/dL, incompletely finishing the 12-week treatment course, or absence from periodical examination sessions.	11	Patients in the omega-3 group consumed 2 omega - 3 capsules daily which contained 1.8 and 2.1 grams of EPA and DHA.
Veselinovic M, et al. 2017[5]	RCT	60	Mean age 63.1 ± 9.6	RA diagnosis based on the ACR 2010 criteria. On dosage of NSAIDs and/or steroids consistently for at least 1 month, and unchanged during the study, while the dose of DMARDs had to be stable for at least 2 months.	Chronic renal, liver or heart ds, DM, smoking, uncontrolled HTN, hyperlipidemia, a family history of cardiovascular ds, premature menopause, a severe folic acid, vitamin B6 or B12 deficiency, and other arthritis.	0	5 g of fish oil with 1 g of concentrated fish oil with 300 mg of DHA, 200 mg of EPA, and 100 mg of other n-3 PUFAs daily after meals.

patient's joints and mark the number of tender joints on a 'joint mannequin.'[9] This review only focused on analyzing the mean change from baseline of joint tenderness as a patient-oriented evidence that matters (POEM), rather than using values from the DAS-28 and VAS.

RESULTS:

Veselinovic et al. carried out a double-blind, randomized controlled trial on 60 female patients with a mean age of 63.1 ± 9.6 years.[5] Each patient had an established diagnosis of RA as determined by the American College of Rheumatology 2010 revised criteria, who were currently on the exact same antirheumatic therapy.[5] This therapy included up to 10 milligrams per day of prednisolone, 15 milligrams per week of oral methotrexate, 10 milligrams per week of folic acid, and non-steroidal anti-inflammatory drugs (NSAIDs) as needed.[5] Alternate RA drug therapy was a component of the exclusion criteria; additional inclusion and exclusion criteria can be found in Table 1. Patient demographics were similar in age, body mass index (BMI), and disease duration. No patients dropped out of the study. Measurements of the tender joint count were taken at baseline with a follow-up assessment at 12 weeks.

The researchers randomly placed patients in three groups of 20 members.[5] The first group took 5 grams of fish oil daily after meals.[5] The capsules were Omega-3 Cardio® gel capsules, each with 1 gram of concentrated fish oil with 300 milligrams of DHA, 200 milligrams of EPA, and 100 milligrams of other n-3 polyunsaturated fatty acids (PUFAs).[5] The control group received the same regimen of antirheumatic drug therapy as the treatment group, without administration of Omega-3 Cardio® gel capsules. The third group received a treatment that is not applicable to this this review. In order to assess the effect of omega-3 fatty acids as adjunctive therapy, joint tenderness was assessed as a subjective measurement by each patient, and the researchers determined the mean change from baseline as demonstrated in Table 2. The mean

change from baseline in the group that received treatment with omega-3 fatty acids saw substantial improvement in joint tenderness. Mean joint tenderness changed from 6.2 to 3.3 in the treatment group and only 5.0 to 4.6 in the control group. The p-value was calculated to be <0.001, solidifying the statistical significance of these findings. Adverse reactions were only found in two patients who experienced gastrointestinal discomfort with mild diarrhea, abdominal pain, and dyspepsia. No other side effects were reported.[5]

Table 2. – Mean Change From Baseline of Joint Tenderness, Veselinovic et al.[5]

Number of tender joints	Omega-3	Control
Baseline	6.2 ± 2.0	5.0 ± 2.0
End of study	3.3 ± 1.5	4.6 ± 1.6
Mean change from baseline	-2.4[LARGE]	-0.4[SMALL]
P-value	<0.001	

Rajaei et al. carried out a double-blind randomized controlled trial on 60 patients, 49 females and 11 males diagnosed with RA according to the Association of Rheumatology America criteria.[6] The mean age was 42.4 ± 7 years and 49 patients successfully completed the study with only 11 dropouts. Detailed inclusion and exclusion criteria are included in Table 1. All subjects were similar in age, sex, drug consumption, and disease duration.[6]

The same maintenance antirheumatic therapy was given to each patient that consisted of 5 milligrams of prednisone twice a day, 200 milligrams of hydroxychloroquine once a day, 0.2 milligrams per kilogram of body weight of methotrexate per week, and 25 milligrams of indomethacin three times a day. Patients were randomly placed in two separate groups, one receiving two omega-3 capsules every day containing 1.8 grams of EPA and 2.1 grams of DHA. The other group received a placebo pill that contained starch and closely resembled an omega-3 product created by Anzan Pharmaceutical Company. All patients reported compliance with the medications given. Assessments of subjective joint tenderness were made at baseline and every four weeks for three months throughout the treatment. The effectiveness of omega-3 treatment

was determined by 50% improvement seen in 89% of the treatment group (experimental event rate, EER= 0.89) and only 13% of the placebo group (control event rate, CER= 0.13) as shown in Table 3. Table 3 shows the number needed to treat (NNT) value of 2, meaning for every two patients with rheumatoid arthritis, at least 1 patient will have a 50% improvement in joint tenderness while taking omega-3 fatty acids, showing a statistically significant improvement (P-value = <0.05). The Absolute Benefit Increase (ABI) of this treatment was calculated at 0.76 as shown in Table 3, demonstrating the increase in improvement of joint tenderness due to the intervention. Table 4 demonstrates the mean change from baseline of joint tenderness in both the placebo and treatment groups. This is calculated to be a decrease in a tender joint count of 19 in the treatment group and only four in the placebo group. Minor adverse reactions from the treatment caused two patients to drop out who complained of vomiting and flatulence.[6]

Table 3. –ABI, NNT, and statistical significance; Rajaei et al.[6]

CER	EER	Absolute benefit increase (ABI)	Number needed to treat (NNT)	P-value
0.13	0.89	0.89-0.13 = 0.76	1/0.76 = 1.3= 2	<0.05

Table 4. – Mean change from baseline of joint tenderness, Rajaei et al.[6]

Number of tender joints	Omega-3	Placebo
Baseline	21	24
End of study	5	20
Mean change from baseline	-19	-4
P-value	<0.05	

Bahadori et al. carried out a double-blind, randomized controlled trial including 24 patients, 23 females and one male, with active RA as diagnosed by the American Rheumatism Association criteria.[9] The mean age was 58 ± 4 years in the treatment group and 59 ± 2 in the placebo group. The initial demographic comparison of the patients was found to be similar in age and weight. In order to be included in the study, each patient was required to complete one month of 10 milligrams per week of methotrexate and 10 milligrams per day of prednisolone.

NSAIDs and paracetamol were allowed as needed and all patients were encouraged to stay on a low AA diet throughout the study. Detailed inclusion and exclusion criteria can be found in Table 1. Only 13 of the 24 patients successfully completed the study.[9]

Researchers randomly placed patients into a treatment group or placebo group and both received inpatient intravenous treatments with follow up at one, two, four, 11, and 22 weeks post therapy. The treatment group received 0.20 grams of fish oil emulsion per kilogram of body weight. Researchers chose Omegaven®, which was a 100 mL containing 6.56 gram of omega-3 PUFA, comprising 2.82 gram of EPA, 3.09 gram of DHA, 0.20 gram α -linolenic acid, and 0.45 gram of docosapentaenoic acid. The control group received an equal amount of 0.9% normal saline intravenously, which was similar in color to the fish oil emulsion. Both groups were treated for four hours every day for 14 consecutive days. A trained physician who determined the number of tender joints through manual palpation performed each assessment and documented the findings on a joint mannequin.[9]

To determine the effectiveness of omega-3 fatty acid treatment compared to the placebo, a mean change from baseline value was calculated as shown in Table 5. The baseline value of tender joints was 18 in the treatment group and 17 in the placebo group. Assessments at week 22 demonstrated that the treatment group had a mean of 15.5 fewer swollen joints and the placebo had only nine fewer swollen joints, demonstrating a statistically significant improvement (P-value = 0.033). Patients in both the omega-3 group and the placebo group experienced adverse

Table 5. - Mean change from baseline of the tender joint count, Bahadori et al.[9]

Number of tender joints	Omega-3	Placebo
Baseline	18	17
End of study-week 22	2.5	8
Mean change from baseline	-15.5	-9
P-value	0.033	

reactions in a very similar distribution, making it less likely that the adverse reactions were caused by the fish oil treatment. Symptoms reported included local infusion reaction, feeling uncomfortable, nausea, diarrhea, headache, and depression.[9]

DISCUSSION:

Rheumatoid arthritis is a common inflammatory arthritis that causes significant pain and discomfort with decreased joint mobility. This review highlights the effectiveness of adjunctive omega-3 fatty acid supplementation on the decrease in the number of tender joints in patients with active RA receiving traditional DMARD therapy. Both Rajaei et al[6] and Veselinovic et al[5] used oral capsules of omega-3 fatty acids with varying amounts of EPA and DHA, while Bahadori et al[9] used intravenous treatment. The effectiveness of omega-3 fatty acids was shown to significantly improve the number of tender joints in each patient population. Baseline DMARD therapy was relatively consistent across studies including methotrexate or hydroxychloroquine, folic acid, and a corticosteroid agent. Although these treatments are not identical, the important point to focus on is the time in which the subjective joint tenderness was recorded. Baseline measurements were made while patients were already taking DMARD therapy. The end measurement was taken only after omega-3 fatty acids were added to their treatment regimen. Although each study delivered treatment in different ways and had varying baseline DMARD therapy, all three study results implied the significant positive impact that adjunctive treatment with omega-3 fatty acids has specifically on joint tenderness.

A limitation of this review was the low number of articles selected for analysis on this topic; future reviews would benefit from more than five randomized controlled trials. The limitations found in all three studies included a low sample size and predominantly female populations. The route of administration and varying amounts of EPA, DHA, and other

ingredients in the omega-3 supplement were also inconsistent across all three studies. The subjectivity of joint tenderness as the POEM leads to increased variability in all three studies. Veselinovic et al discussed the lack of a blinded placebo control group as a limitation, which was chosen due to the ingredients in most placebo pills having a possible impact on study outcome.[5] Bahadori et al had a large number of dropouts combined with the smallest sample size out of all three studies, making it difficult to relate the research findings to the general population. Lastly, a large limitation that is difficult to control in this research is the varying impact that traditional DMARD therapy has on each individual patient. Rather than fish oil supplementation causing improved joint tenderness alone, it's likely a combination of both DMARD therapy and fish oil improves the symptoms of joint tenderness.

Omega-3 fatty acids are sold as fish oil tablets and contain varying concentrations of EPA and DHA. This affordable product is readily available in most drug stores in the United States and is sold as an over-the-counter medication not covered by insurance. Few omega-3 fatty acid supplements are sold as prescription products; however, Lovaza® is a combination of EPA and DHA ethyl esters, is one example that may be covered by insurance.[10]

CONCLUSION:

All three studies provided statistically significant evidence suggesting the positive impact that omega-3 fatty acid supplementation has on joint tenderness on patients with active rheumatoid arthritis. The number of tender joints decreased substantially in each treatment group that received fish oil as adjunctive therapy to traditional DMARD therapy when compared to the control groups. Future research should aim at broadening the sample populations including more research on males with RA and increasing the sample size. Ideally, one large study with several

hundred adult RA patients of both genders diagnosed based on the same criteria, treated with the same baseline DMARD therapy, and receiving the same concentrations of EPA and DHA in the fish oil supplementation would provide more valid results. Controlling for extraneous factors that impact the results of this intervention will be difficult but could provide beneficial evidence to improve both joint function and tenderness in patients with RA.

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